

**Remarks****A. Amendments**

Claims 4 and 10-19 are pending in this application. Claims 4, 10, 13, 14 and 19 are amended. Upon entry of these amendments, claims 4 and 10-19 are under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Claims 4 and 10 are amended to remove reference to analogs and solvates.

Claims 13, 14 and 19 are amended to correct typographical errors.

**B. Information Disclosure Statement**

The Examiner, at page 2 of the Office Action, states that the Information Disclosure Statement filed on October 19, 2004 (the "IDS") fails to comply with 37 CFR § 1.98(a)(2). Applicant submits herewith a legible copy of each non-patent reference listed on the IDS and respectfully requests that the Examiner consider these references.

### **Patentability Arguments**

#### **A. The rejections of claims 4 and 10-19 under 35 U.S.C. § 112, first paragraph should be withdrawn.**

At item 4 on page 2 of the Office Action, the Examiner rejects claims 4 and 10-19 under 35 U.S.C. § 112, first paragraph for lack of enablement. At page 4 (item 4) of the Office Action, the Examiner has alleged that the claims are not enabled because the “scope of the instant claims encompasses treatment of multitude of disorders or conditions that may have unrelated manifestation.”

Applicant respectfully submits that the Examiner has mischaracterized the scope of the instant claims. Contrary to the Examiner’s assertions, the scope of the instant claims do not “encompass treatment of multitude of disorders or conditions that may have unrelated manifestation.” Rather, the instant claims are directed to methods for “treating wasting”. The MedlinePlus Medical Encyclopedia defines the term “wasting” as “muscle atrophy” which is further defined as “the loss of muscle tissue resulting from disease or lack of use.” This definition is consistent with the use of the term in the instant specification. *See, e.g.,* paragraph [0068]. Wasting is a common manifestation of the disorders cited by the Examiner. Thus, it is irrelevant whether “a single underlying mechanism ties together all of the seemingly unrelated manifestations” of such disorders. The Examiner, at page 2 of the Office Action, has admitted that the specification is “enabling for treating a symptom of wasting.” As that is precisely what is claimed, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 4 and 10-19 under 35 U.S.C. § 112, first paragraph.

At page 5 (item 4) of the Office Action, the Examiner characterized the claim terms “analogs” and “solvates” as encompassing a breadth not supported by the specification. The claims have been amended to delete any reference to “analogs or solvates” of cis- or trans-clomiphen. Applicant respectfully submits that these amendments overcome the rejection for lack of enablement.

**B. The rejection of claims 4 and 10-19 under 35 U.S.C. § 103 should be withdrawn.**

At item no. 5 on page 7 of the Office Action, the Examiner rejects claims 4 and 10-19 under 35 U.S.C. § 103(a) as being unpatentable over Tenover *et al.* (hereinafter, “Tenover”). The Examiner characterizes Tenover as teaching the activity of clomiphene (containing between 30% and 50% of the cis-isomer) in increasing serum testosterone levels in the body. The Examiner alleges that Tenover differs from the instant invention in (1) the use of the claimed composition in treating wasting in a mammal, (2) the specific ratio of trans- and cis-clomiphene, and (3) the specific dosage amounts. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to “modify the Teachings of Tenover with reasonable expectation of success to extend the usage of the claimed composition in human” in light of the disclosure of Baird *et al.* (hereinafter “Baird”), characterized by the Examiner as teaching administration of clomiphene substantially free of the cis-isomer to a mammal, and further in light of the instant specification’s disclosure that testosterone therapy has positive effects on muscle-mass, bone, memory, libido and sense of well being in HIV-infected men. Further, the Examiner asserts that “determination of the specific ratio of cis-isomer and trans-isomer having optimum therapeutic index is considered obvious task for the skilled artisan.” Applicant respectfully disagrees and submits that the Examiner has failed to provide a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references or in the knowledge available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Third, there must be a reasonable expectation of success. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicant respectfully submits that the cited references, in failing to provide either a motivation to combine or a reasonable expectation of success from the combination, provide at least two independent and legally sufficient reasons to withdraw the rejections under 35 U.S.C. § 103(a).

**1. The Cited References Fail to Teach or Suggest All the Claim Limitations**

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. The prior art references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. See MPEP § 2141.

Applicant respectfully submits that the cited prior art, in combination, fails to teach or suggest a method of treating wasting in a mammal comprising the use of a composition comprising cis- and trans-clomiphene wherein the ratio of trans- to cis-clomiphene is greater than 71/29.

Baird teaches that administration of clomiphene substantially free of the cis-isomer to a female is useful for inducing ovulation. The instant claims are directed to a method of treating wasting by administering a composition that elevates serum testosterone levels. Applicant respectfully submits that Baird is nonanalogous art which has no pertinence to the instant invention. *See* MPEP § 2141.01(a). One of ordinary skill in the art would not reasonably have expected to solve the problem of treating wasting by considering a reference dealing with the induction of ovulation. Therefore, Applicant respectfully submits that Baird is improperly relied upon by the Examiner.

Tenover teaches that administration of clomiphene citrate is capable of elevating testosterone levels in human males. Tenover does not disclose the administration of cis- or trans-clomiphene nor does Tenover suggest altering the ratio of clomiphene isomers.

The instant specification, at paragraph [0008], discloses that “testosterone therapy is beneficial” in treating wasting but warns that “high amounts of testosterone increase the risk of cardiovascular disease and benign prostate hyperplasia.” The instant invention provides a method of treating wasting by administering a composition comprising cis- and trans-clomiphene wherein the ratio of trans- to cis-clomiphene is greater than 71/29, thus avoiding the side-effects associated with testosterone therapy.

The analogous prior art cited by the Examiner thus discloses: (1) the ability of clomiphene citrate to elevate testosterone levels in males; and (2) the administration of testosterone for treating wasting. No combination of the analogous art of record, even if supported by a motivation to combine, discloses the use of a composition comprising cis- and trans-clomiphene wherein the ratio of trans- to cis-clomiphene is greater than 71/29 for treating wasting in a mammal. As elaborated *infra*, in order to arrive at the invention as presently claimed, one of ordinary skill in the art, armed with the combination of prior art cited by the Examiner, would be required to make several inventive leaps to fill in the missing limitations. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

2. The Cited References Fail to Provide Motivation or Suggestion to Combine the References

The Examiner has asserted that one of ordinary skill in the art would be motivated to combine the references because they are “drawn to same technical fields and pertinent to the problem which applicant concerns about [*sic*]” but the Examiner has failed to point to any motivation or suggestion for combining the references. In providing such a motivation, the Examiner must consider the cited reference as a whole, including portions that would lead away from the claimed invention. See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Tenover describes the administration of clomiphene citrate to stimulate gonadotropin (FSH, LH) secretion in order to assess the hypothalamic or pituitary control of testicular function in elderly men. Nowhere in Tenover is it revealed that clomiphene citrate is a racemic mixture of cis- and trans-clomiphene, nor is any attempt made to distinguish the potential endocrine effects of cis-clomiphene versus trans-clomiphene or ratios thereof. On the contrary, Tenover acknowledges that clomiphene’s “exact mechanism of action is uncertain” with most evidence pointing to “a hypothalamic target site where it appears to displace endogenous estrogens from hypothalamic receptors.”

Baird discloses the treatment of female infertility by administering clomiphene and reports that removal of cis-clomiphene from the racemic mixture (generally 38% cis and 62% trans according to Baird, page 2, lines 33-34) currently administered for the induction of ovulation allows the effective use of a lower dosage without affecting the ovulation rate. The effect of clomiphene, trans-clomiphene or cis-clomiphene on testosterone levels is not mentioned in Baird nor is there any suggestion or motivation to apply the teachings therein to treat wasting in a mammal by administering clomiphene wherein the ratio of trans-clomiphene to cis-clomiphene is greater than 71/29. Additionally, as noted *supra*, Baird is drawn to a nonanalogous art and is not relevant to the problem with which the instant invention is concerned (i.e.: ovulation *vis a vis* wasting).

Further, the findings of Baird contradict at least two peer-reviewed studies which teach away from the use of clomiphene wherein the ratio of trans-clomiphene to cis-clomiphene is greater than 71/29. On page 2, lines 51-52, Baird points to a study that directly contradicts Baird’s own teachings: “According to Mikkelsen *et al.*...the Zu (cis) isomer is the active one.”

Applicant also directs Examiner's attention to paragraph [0013] of the instant specification which points out that "Ernst *et al.*...attribute the effect of the drug [clomiphene] on ovulatory activity to both forms stating that the mixture is more effective than trans-clomiphene alone." The uncertainty in the art is perhaps best summarized at page 2, lines 12-13 of Baird: "These conflicting and sometimes paradoxical results have lead to considerable confusion concerning the mechanism of action of clomiphene." In light of the aforementioned, the Examiner has failed to provide a rationale for why one of ordinary skill in the art would be motivated to combine said references and respectfully requests withdrawal of the rejections for obviousness under 35 U.S.C. § 103(a).

### 3. The Cited References Fail to Provide a Reasonable Expectation of Success

Similar to the failure of the Examiner to provide a motivation or suggestion to combine the above references, the Examiner fails to provide a rationale for why one of ordinary skill in the art would have a reasonable expectation of success given the studies teaching away from the use of clomiphene wherein the ratio of trans-clomiphene to cis-clomiphene is greater than 71/29. Even assuming *arguendo*, that the references do provide a motivation to combine, given the complexity of the endocrine system, the skilled artisan would not expect that clomiphene wherein the ratio of trans-clomiphene to cis-clomiphene is greater than 71/29 would be more effective than clomiphene citrate in treating wasting in a mammal. First, Tenover makes no attempt to attribute the observed increase in testosterone to either clomiphene isomer. Second, Baird, at page 2, lines 37-39, teaches that each clomiphene isomer has the capacity to interact with estrogen receptors and exhibit estrogenic or antioestrogenic effects depending on the kind of tissue and the dose, indicating the difficulty of extrapolating data obtained on the effect of removing the cis-isomer on ovulation rate to that of serum testosterone levels. Finally, as noted *supra*, multiple studies in the art attributed the effects of clomiphene citrate to the cis-isomer.

In light of the aforementioned, Applicant respectfully submits that the Examiner has failed to establish that one of ordinary skill in the art would have had a reasonable expectation of success and therefore Applicant respectfully requests withdrawal of the rejection for obviousness under 35 U.S.C. § 103(a).

### 4. Secondary Considerations: Unexpected Results

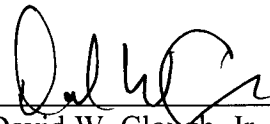
In addition to the arguments presented above, Applicant submits that the instant claims are nonobvious over the prior art based on Unexpected Results. Figure 3 of the instant application demonstrates that enclomid is more than twice as effective as clomiphene citrate in elevating serum testosterone levels. Based on the disclosures of Tenover and Baird, the skilled artisan could expect, at best, that removal of cis-clomiphene would have no effect over clomiphene citrate on serum testosterone levels. However, to arrive at this expectation, the skilled artisan would have to ignore: (1) confusion in the art, alluded to by the Examiner's own prior art citations regarding which clomiphene isomer is the active one; and (2) the fact that Baird is directed to an entirely nonanalogous art and therefore cannot provide the foundation on which to predict the results achieved by the instant invention. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a).

**Conclusion**

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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